Immunology of Prion Neuroinvasion: Importance of Secondary Lymphoid Organs in the Early Stages

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Introduction

Prions (PrP^{sc}) are a misfolded form of the endogenous prion protein PrP^{c} which can cause transmissive and fatal neurodegenerative diseases in humans. When orally acquired, first steps in prion neuroinvasion essentially depend on exploiting secondary lymphoid organs in order to replicate and enter the enteric nervous system (ENS) to reach the central nervous system (CNS). The gut associated lymphoid tissue (GALT) plays a key role in the process, allowing the agent to accumulate, replicate and disseminate.

Aims

Provide an insight, from an immunological point of view, into what is known of the prion-cell interaction from the intestinal trans-epithelial crossing to prion delivery to the ENS during neuroinvasion, focusing on GALT importance.

Results

1 Trans-epithelial crossing

Prions need to cross the Follicular Associated Epithelium (FAE) to reach GALT's Peyer's patches (PPs) and mature Isolated Lymphoid Follicles (mILFs) (**Fig. 2**), where accumulation is most relevant[1]. Caption is accomplished by **M-cells** and **enterocytes**, where Laminin receptor (LPR/LR) - expressed in their apical brush - may have a key role, in a PrP^{c} independent manner; possibly through endocytic vesicles.

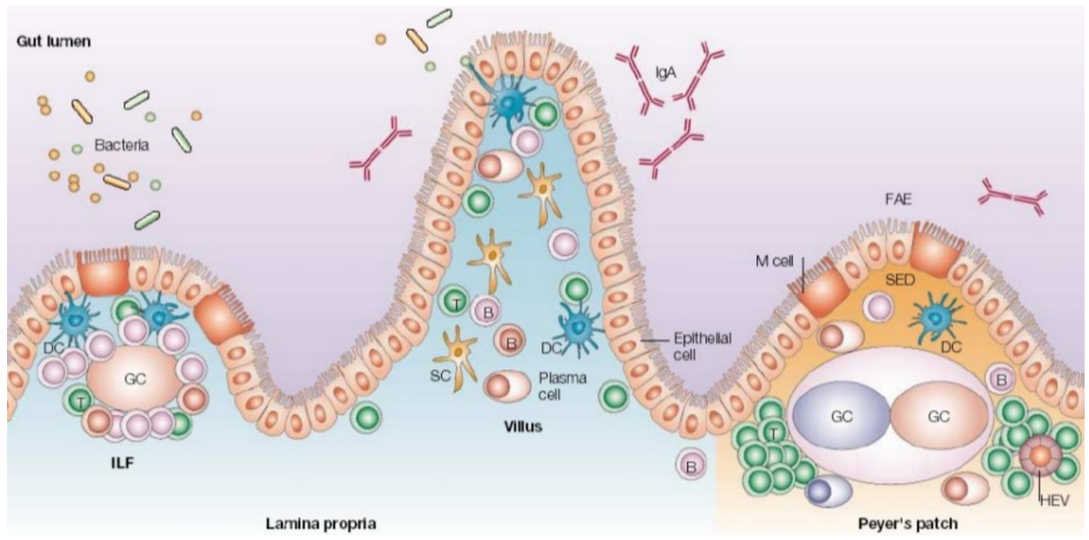

Fig. 2[2] – Representation of GALT, including PPs and ILFs. Abbreviations: SC – Somatic Cell. T- Lymphocyte T. B – Lymphocyte B.

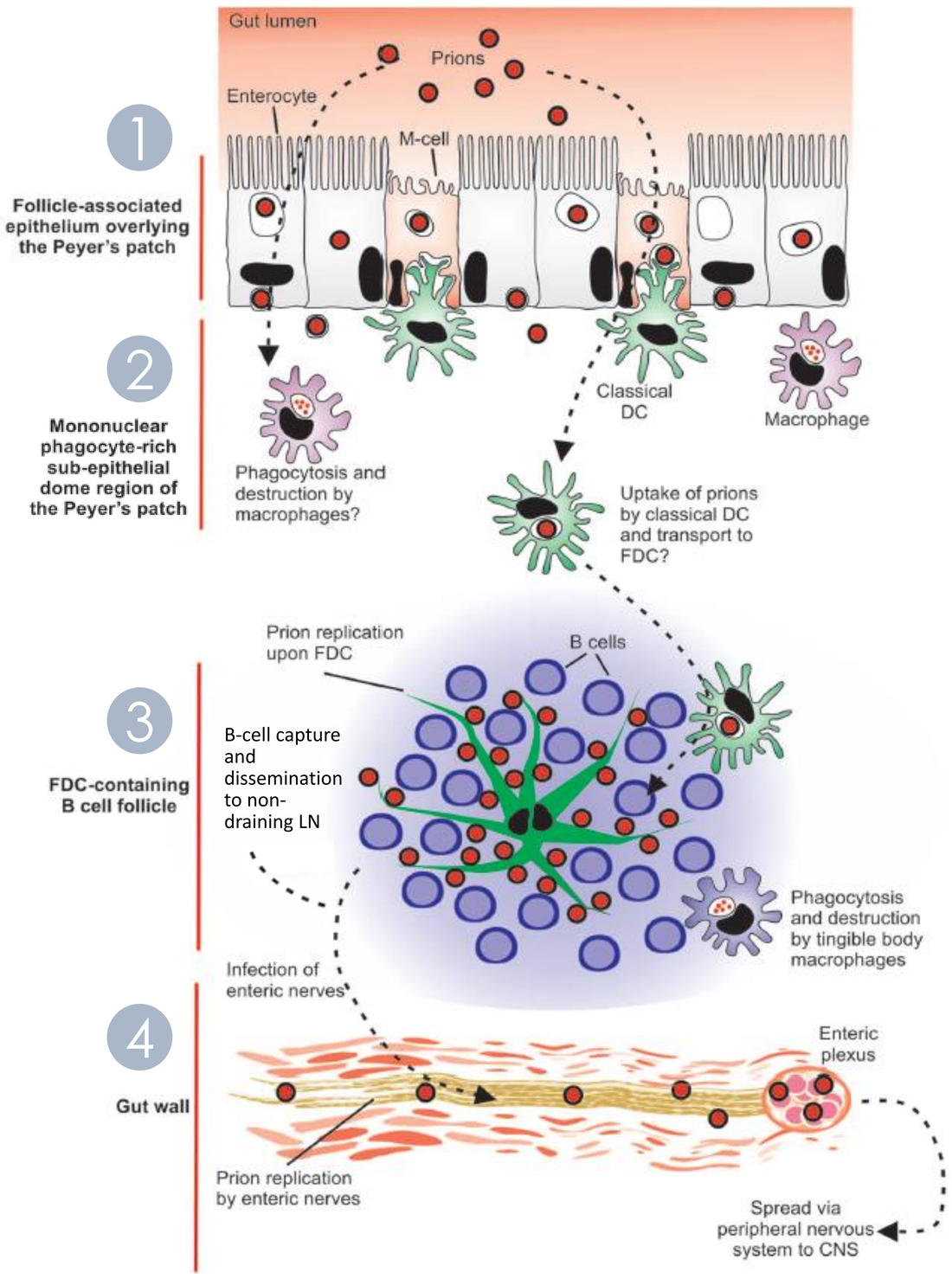

Fig. 1[3] – Scheme of first steps in orally acquired prion neuroinvasion.

2 Transport to Secondary Lymphoid Organs

Once in the Sub-Epithelial Dome (SED), prions delivered by M-cells will arrive to PPs and mILFs through **$CD11c^{+}$ $CD11b^{-}/CD8\alpha^{-}$ CXCR5-expressing classical Dendritic Cells (DCs)**, which can acquire the agent by Tunnelling Nano Tubes (TNTs), most probably by trapping it complement-opsonized[3]. Tingible-Body Macrophages can likewise acquire prions, allegedly from enterocytes, but unlike DCs they might degrade them maintaining a *plateau* state of prion accumulation competing with prions replicating among Follicular DCs (FDCs)[4].

3 FDCs in Germinal Centres (GCs) and B-cells

DCs migrate to GCs through CXCL13-CXCR5 signalling. There FCDs acquire prions by stripping the classical-pathway-complement opsonized complexes (where C3 and C1q are essential) from DCs - or in an indirect manner by B-cell intermediators - [5].

FDC in GCs accumulate and replicate prions on their surfaces aided by B-cells which provide Lymphotoxins and TNF for FDC-network maintenance and formation of hypertrophic dendrites, which will provide an optimal environment for prion replication: By Inducing a strong GC response by the B-cell CD21/35) and by further presentation to **other B-cells, which will disseminate prions to non-draining LNs**[6].

In MLNs where prion accumulation can be FDC independent, **HEVs** serve as entry point for prion-harbouring macrophages, which are thought to accumulate prions thanks to their inability to destroy them at high enough titters, and B-cells which disseminate them. HEVs are maintained by LTβR signalling, which is provided by not only B-cells but also DCs[7].

4 Invasion of ENS

Prions reach the CNS by **invading the ENS innervating SLOs**, being delivered to nerves by DCs or FDCs[8] most probably by cell-cell contact through TNTs or by PrP^{sc} loaded exovesicles.

Conclusions

Orally acquired prions use immune compounds to arrive to the CNS and GALT has a key role in the process. DCs and FDCs constitute the greatest crucial point, being the most exploited cells by the agent. Separately, prion uptake by M-cells is the first essential step, and would constitute an interesting target for new therapies. As current treatment strategies involving inhibitors targeting initial uptake and accumulation of prions severely reduce disease susceptibility, further understanding of the DC and FDC-prion interaction, and the still hypothesized invasion steps, could lead to novel therapeutic strategies or new factors affecting the pathology.

References

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